Update and a new statement of the electromagnetic coupling hypothesis to explain the translocation of protons in mitochondria, bacteria and chloroplasts

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Theoretical Communication

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Summary

With the aim of proposing a mechanism that explains how the transport of electrons in some biological membranes is able to move ions, mainly protons, even against their concentration gradient, one of my works, entitled "An electromagnetic coupling hypothesis to explain the mechanism of proton translocation in mitochondria, bacteria, and chloroplasts," was published more than 25 years ago in the journal Medical Hypotheses, 1996. Time has passed, and the subject continues to be very controversial, however, technological development, especially electron microscopy and nanotechnology, has made it possible to obtain new scientific evidence that not only supports this hypothesis but also enriches the original approach with a new precept: the electromagnetic fields generated by the transport of electrons in biological membranes, besides influencing the movement of ions found in the surrounding environment, are also responsible for most of ultrastructural changes observed by electron microscopy and play a very important role in the redistribution and positioning of proteins within the membranes in which processes such as cellular respiration and photosynthesis take place.

1. In the immediate aftermath.

More than 25 years have passed since the publication of the electromagnetic coupling hypothesis to explain the mechanism of proton translocation in mitochondria, bacteria, and chloroplasts [1]. Some authors, such as Belevich [2], Rottenberg [3], and Morelli [4], among many others, have published extensive reviews on the subject, describing many theoretical models all based on conformational changes of proteins involved in the process and induced by redox reactions, concluding that many of these models have been refuted and that there is still no widely accepted single theory.

It was not until the year 2000, that researchers Kohane and Tiller [5] reported some important results on the effects of electromagnetic fields (EMFs) in *Drosophila melanogaster*, describing how they can influence cellular energy metabolism and taking into account, for the first time the electromagnetic coupling hypothesis (EMCH) to explain some of their findings. In their work, they suggest that the pathway by which EMFs can affect biological systems is probably through the influence of the magnetic vector potential on the activity of the electron transport system (ETS).

Later, in 2009, Funk and colleagues [6] stated that a change in paradigm took place concerning the endogenously produced static electric fields of cells and tissues and exposed several scientific evidences taking into account the presence of electromagnetic fields in histochemistry and cytochemistry experiments. They pointed out that all systems in an organism from the molecular to the organ level are more or less in motion; therefore, in living tissue, we mostly find alternating fields as well as a combination of electric and magnetic fields normally in the range of extremely low-frequency EMFs.

They described how an electric field between the blastomeres, which is induced by an asymmetrical flow of H^+ ions generated by ATPase enzymes in the early embryo, appears to be a driving force to dislocate small molecules such as serotonin. In this scientific work, the authors also described very important considerations in order to explain their findings, as, for example: 1) Electrons, protons and ions can be conduction charges and the movement of the conduction charges builds up a current the which produces new fields; 2) Thermal excitation causes random motion of the conduction charges, and the force due to an applied field superimposes a slight movement in the direction of the force on this random movement that did not exist before the electric field was applied.

These scientific works carried out during the first years after the EMCH publication are in complete correspondence with its statements. The movement of electrons through the different electron transfer systems in mitochondria, bacteria and chloroplasts, similar to any other current of electrons, induces electromagnetic fields that exert forces on the electric charged particles (protons and all the other ions) in the media near these fields, modifying their random motion and increasing the probability of movement from one side of membranes to the other, even against the concentration gradient.

2. Is there any electrical current self-engendered inside the mitochondrial inner membrane?

In 2011, Archederra and colss [7] developed an approach for directly electrochemically assaying mitochondrial metabolic activity as a function of metabolic substrate to determine drug toxicity. By wiring mouse mitochondria to a carbon electrode surface, electrons were intercepted before they reach Complex IV, the terminal step of the electron transfer system.

The electrons are rerouted to a separate electrode of the electrochemical cell, enabling the direct measurement of the electrical current and potential of the mitochondria during the oxidation of substrates such as pyruvate and fatty acids.

Recently, in 2018, Wikstrom and his group [8] studied oxygen activation and energy conservation through cytochrome *c* oxidase in depth and analyzed data from multiple scientific papers on how the transfer of electrons between the metallic centers of proteins involved in redox reactions takes place, concluding that the protein composition of the medium is relatively unimportant for the transfer of electrons between the groups and that it is the distance and not the medium composition that is the main determinant of the rate of electron transfer.

More recently, in 2019, Wolf and cols. [9] described how an elongated mitochondrion stained with a membrane potential($\Delta\Psi_{\text{mt}}$)-dependent dye appears to instantaneously lose its $\Delta\Psi_{\text{mt}}$ following laser-induced damage to a small (≤ 0.5 μm^2) region, suggesting that a mitochondrial filament is analogous to a power cable, where, if one part is compromised, the voltage will simultaneously collapse across its entire length, and how individual cristae within the same mitochondrion display different membrane potentials and are functionally independent. They concluded that the tendency for one mitochondrion to exhibit localized depolarization indicates that a single organelle does not resemble an electrical wire but rather appears to function more like a configuration of interconnected batteries. They also described how hyperpolarized and depolarized mitochondrial inner membrane (mtIM) potentials are associated with different states of respiration. While an increased rate of ATP synthesis dissipates $\Delta\Psi_{\text{mt}}$, a decrease in ATP synthesis may result in hyperpolarization and increased reactive oxygen species (ROS) production.

Also in 2019, Meysman and cols. [10] studied biological electron transfer but not in nanometre distances, suggesting that electrical currents can run along centimeter-long cable bacteria (multicellular microorganisms in the Desulfobulbaceae family that display a unique metabolism, in which electrical currents are channeled along a chain of more than 10,000 cells) and demonstrating that cable bacteria conduct electrons over centimeter distances via highly conductive fibers embedded in the cell envelope.

Posteriorly in 2021, Boschker et al. [11] combined high-resolution microscopy, spectroscopy, and chemical imaging of individual cable bacterium filaments to demonstrate that the periplasmic wires consist of a conductive protein core containing a sulfur-ligated nickel cofactor surrounded by an insulating protein shell layer and that the involvement of nickel as the active metal in biological conduction is remarkable, suggesting a hitherto unknown form of electron transfer that enables efficient conduction in centimeter-long protein structures.

In the past year 2022, Gomila and coworkers [12] observed that electron transfer between mitochondrial cytochrome *c* and the cytochrome *c*1 subunit of cytochrome *bc*1 can proceed at a long distance through the aqueous solution. They demonstrated that phosphorylation impairs long-range electron transfer by shortening the long-distance charge conduit between the partners.

These results, pointing all of them to the importance of distances in the transport of electrons and comparing filamentous mitochondria with energy-transmitting cables or electrical wires, added new evidence supporting a basic assumption of the electromagnetic coupling hypothesis: an electric current emerges when the electrons pass through any electron transfer system and therefore, just like in any other current of electrons, electromagnetic fields are generated as it was described by Oersted more than 200 years ago in 1820 [13].

3. Usefulness of the electromagnetic coupling hypothesis to explain some biological effects of electromagnetic fields.

On the other hand, in 2014, Burlaka A. et al. [14] reported some qualitative and quantitative disorders of the ETS in mitochondria exposed to ultrahigh-frequency electromagnetic radiation using electron paramagnetic resonance methods and concluded that alterations in mitochondrial ETS in cells of the liver and aorta are more pronounced when pulsed electromagnetic radiation is used, which causes an increase in the rate of generation of superoxide radicals in all samples.

Additionally, in 2016, Vian [15] described how some authors have proposed that the effects of light in plants are produced not only through chromophores but also through alternating electric fields that are induced in the medium, capable of interacting with polar structures by means of dipole transitions and indicating the ATP/ADP ratio, ATP synthesis and the regulation of ionic calcium as possible targets.

In 2018, also trying to explain how electromagnetic radiation affects cell life in Microcystis aeruginosa photosynthesis, Chao Tang and his collaborators [16] found that the type of electromagnetic field used in their study may affect the function of photosynthetic pigments, the electron transfer process, and the photosynthetic phosphorylation.

If the precepts of EMCH are taken into account, these results of scientific investigations about the effects of electromagnetic radiation in cell life could be better explained, and above all, it could be better understood why cellular respiration and photosynthesis are precisely the most important targets on which electromagnetic fields can act in biological systems.

In 2015, De Vries and coworkers [17] stated that the chain of iron–sulfur centers is not just a simple electron-conducting wire because it regulates the electron-tunneling rate, synchronizing it with conformation-mediated proton pumping and making possible a more efficient energy conversion.

Once again, if the EMCH is taken into account, the nexus between the flux of electrons through the chain of iron–sulfur centers and the synchronized conformational changes observed is the electromagnetic fields induced by the movement of the electrons through the components of the electron transfer system.

4. More experimental evidence and a new precept of the electromagnetic coupling hypothesis

In 2016, Zablotskii and his coauthors [18] trying to explain how magnetic fields affect cell life, described some results:-1) When a high-gradient magnetic field is applied to a cell, the magnetic gradient force acts on ions and can either assist or oppose their movement through the membrane; 2) Static homogeneous magnetic fields can also affect the diffusion of biological particles through the Lorentz force; and 3) Due to the difference in the magnetic susceptibilities of proteins and lipids, the membrane receptor proteins are attracted to the area with the highest magnetic field gradient generated by a chain of magnetic nanoparticles placed on a cell membrane.

This work also describes how the mitochondrial inner membrane potentials polarize and depolarize according to the different states of cellular respiration. While the increase in ATP synthesis dissipates the membrane potential, the decrease in ATP synthesis can cause hyperpolarization and increase the production of ROS.

In 2018, Schwartz and colleagues [19] suggested that electromagnetic fields can affect both, macromolecule charge distribution and spatial position within a cell volume, and this phenomenon can result in elevated and opposite electric fields that can be sensed locally within a cell. They proposed that physical forces interfere with the cell's metabolism, mostly at the level of the mitochondria.

Scholkmann [20] (20 years after publication of the EMCH) carried out a very important scientific work about long-range physical cell-to-cell signaling via mitochondria inside membrane nanotubes and took into account the EMCH in order to explain some experimental findings. In this investigation, he demonstrated that there was convincing experimental evidence about mitochondria how the source of radiating high-frequency electromagnetic fields in the optical spectral region measured as spontaneous (low-level) chemiluminescence or ultra-weak photon emission. He also exposed how modern super-resolution microscopy made it possible to demonstrate that mitochondria exist in different forms, ranging from spherical or ellipsoid shapes to long filamentous or tubular structures that can form also branched networks, and, in addition, the structure of the mitochondrial inner membrane (cristae) shows also different morphologies strongly determined by the metabolic state.

From my point of view, all these findings support the idea that there are engendered electric currents inducing electromagnetic fields in the mitochondrial inner membrane, which play a role in the movement of charged molecules and are also responsible for the different morphologies that have been found by using electronic microscopy technologies depending on the metabolic state and, therefore, of the electron transfer system activity.

Three years ago, in 2020, Meng Wu and coworkers [21] affirmed that interaction between ETS complexes and ATP synthase is unnecessary, while the battery, like the mitochondrial inner membrane, stores the energy needed, and that this is inconsistent with the previous idea that the respiratory components were rigidly coupled as a functional unit, which requires complicated regulation of stoichiometries at each step.

One year later, in 2021, Bennett and Onyango [22], investigating the pathophysiology of some neurodegenerative diseases, explained how nonhydrated protons are apparently involved in driving the ATP synthase rotor and how anatomical proximity is needed between the rotor docking sites of this enzyme and the proton pump sites. They also reported that what most affected ATP synthesis was the inhibition of electronic transfer in the ETS.

Based on recent experiments demonstrating that chloroplast ATP synthase, like those of mitochondria and bacteria, requires a membrane potential for ATP synthesis, Dimroth et al. [23] concluded that the membrane potential and proton gradient are not equivalent under normal operating conditions far from equilibrium, and these conclusions are corroborated by the finding that only the membrane potential induces a rotary torque that drives the counter-rotation of the a and c subunits in the F(o) motor of *Propionigenium modestum* ATP synthase.

Last year, in 2022, Bombek and Čater [24], after recognizing the need to update the chemiosmotic theory due to the numerous questions still unresolved, proposed that the coupling of cellular respiration with ATP synthesis is imperfect and that the energy consumption of mitochondria persists even after inhibiting ATP synthesis, confirming the existence of possible uncoupling mechanisms that generate thermal energy without ATP synthesis.

All these results provide new knowledge that supports and enriches the electromagnetic coupling hypothesis and allows adding a new precept: It can now be stated that the electromagnetic fields generated by the electron transfer in the mitochondrial inner membrane are not only responsible for the morphological changes that have been observed in the different states of the mitochondrial activity, but also contribute to the reorganization of proteins participating in the process of oxidative phosphorylation (both, those that are involved in the transfer of electrons, and the ATP synthase that needs to be coupled and adjust its anatomical positioning in order to carry out its action). This approach can also be argued if one takes into account long-established scientific knowledge such as the mobility of proteins under the action of electric fields in routine electrophoresis techniques [25] and that most of the proteins involved in the electron transfer systems are metalloproteins containing transition metals such as Fe and Cu with magnetic and paramagnetic properties [26].

5. Nanotechnology will have the last word.

In 2021, the Hicks group [27], using a carbon nanotube inserted into a cell membrane that can act as a bipolar nanoelectrode, demonstrated that the flow of electrons through membranes can be controlled by external electric fields across membranes, which offers the possibility of using bipolar electrodes to alter cell behavior through wireless control of electron transfer in membranes, suggesting that in the future, wireless communication with cells would be possible through bioelectronics treatments.

Finally, according to Patra M. and Maiti S. [28], the study of electronic transport through single molecules has been the object of intense research, and it has been possible thanks to the development of nanotechnology. In their recent work trying to control the local magnetic field in a molecular junction, a circular current is established in the rings of different molecular structures, namely, benzene, naphthalene and anthracene which induces a magnetic field at its center, allowing a direct coupling between two electrodes due to their proximity. They also describe how it can regulate circular current as well as magnetic field for a wide range without disturbing any other physical parameters.

As seen, the number of papers published in which electromagnetic fields are used and studied in the intracellular media and, what is more incredible, in the intramolecular environment by means of highly sophisticated nanotechnologies is increasing, and will make it possible to accept or reject definitively the electromagnetic coupling hypothesis that already exceeds 25 years of enunciation.

Abbreviations

EMCH	electromagnetic coupling hypothesis	mtIM	mitochondrial inner membrane
EMFs	electromagnetic fields	ROS	reactive oxygen species
ETS	electron transfer system		

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